COMMENTARIES

Goals for Research on Bipolar Disorder: The View from NIMH

Bipolar disorder is common (affecting an estimated 1.5% of the adult population), serious, disabling, and inadequately researched. A high priority of the National Institute of Mental Health (NIMH) is to encourage both basic and clinical investigators to focus their research efforts on bipolar disorder. In this overview, I focus on six areas in which urgent questions and opportunities stand out: genetics, the mechanisms of mood regulation in the brain, animal models, pharmacologic treatment development, psychosocial interventions, and clinical trials. I will not discuss areas in which research is on a steady, successful course, and thus less in need of intervention.

Genetics

It is absolutely critical that we discover the genes that confer risk for bipolar disorder and other mood disorders. Why are such "risk genes" essential research tools? First, they will provide us with independent variables by which we can delineate more homogeneous groups for research and treatment intervention. Second, the time during brain development at which these genes are expressed and the functions of the proteins that they encode will afford clues to understanding brain function in bipolar disorder; such data will also sharpen our search for potentially modifiable environmental factors that interact with genes to influence the onset and course of illness (Hyman 1999). Such genetic tools should help revitalize psychiatric epidemiology, moving it beyond counting people with particular syndromes to a focus on understanding disease risk. Third, as elaborated below, genes will provide clues to novel drug targets that could direct therapies at underlying pathophysiologic processes.

From the beginning of the modern era of psychiatric diagnosis it had been hoped that clustering of symptoms and signs, course of illness, family history, and perhaps treatment response would coalesce to provide valid disease entities. This, unfortunately, has not proven to be the case. There are clinically important phenotypes—for example, unipolar depression and rapid cycling that appear in bipolar pedigrees—but they do not appear to breed true (Tsuang and Faraone 1990). This is consistent with findings from twin studies and also from molecular genetic linkage analyses demonstrating that bipolar disorder is genetically complex. It appears that multiple genetic loci, each contributing relatively small increments of risk, interact with nongenetic factors—including both stochastic factors that come into play during brain development

and specific environmental risk factors—to produce illness and to modify its course. The potential interaction of many different disease vulnerability genes and course modifier genes could explain some of the anomalies described above in disease transmission within families.

The failure, to date, to replicate any genetic linkages to bipolar disorder with adequate certainty is no different from the situation with most of the other common, genetically complex disorders that afflict humanity. There is, of course, little solace in this, as all of medicine faces the difficult task of discovering genes that contribute relatively small effects and then understanding how they interact with each other, in many cases in nonlinear fashion, to alter end organ function. There is consensus in the field that future progress in risk gene discovery will require the collection and analysis of large numbers of bipolar pedigrees from outbred populations, as well as pedigrees from genetically isolated populations. The National Institute of Mental Health is currently funding large collaborative projects in the U.S. and abroad in Latin America, Europe, the Mideast, and the Far East. An important aspect of the NIMH approach to human genetics research is a requirement that investigators ultimately place their DNA samples and phenotypes in the public domain, so that as new ideas become available they can be rapidly tested. Further information is available on the worldwide web (NIMH 2000). The hope is that these large datasets will be in place as the technology to analyze them matures.

One critical component of the technologic platform that will ultimately permit successful identification of risk genes for bipolar disorder and other genetically complex disorders is the complete sequence of the human genome. This sequence should be available, at least in draft form, from both the public Human Genome Project and from industry by now. This reference sequence must be complemented, however, by extensive cataloging of human genetic variation, since, after all, the goal of genetics is to relate sequence variation to phenotype. Fortunately, multiple collaborations supported by private and public funds now are ongoing to identify variation throughout the human genome and within that approximately 4% of the genome that comprises genes (Chakravarti 1998). These efforts are focusing on a type of DNA sequence variation in which a single nucleotide base is altered, so-called single nucleotide polymorphisms (SNPs; Chakravarti 1998; Collins et al 1997; Lander 1996). New methods are being developed for cheap, very high throughput analysis

of SNPs using such technologies as DNA chips or mass spectrometry. Such developments may make possible whole genome studies, by which associations may be detected between SNP variants and bipolar disorder (Kruglyak 1999; Risch and Merikangas 1996). Of greatest interest to researchers studying abnormal brain circuits in bipolar disorder will be those protein-altering SNPs that occur within genes expressed in the brain.

Success in genetics will revitalize epidemiology and nosology, and will provide critically important tools with which to understand the pathogenesis of bipolar disorder and design new therapies.

The Neural Substrate of Mood Regulation

If genes represent a critical tool for investigating pathogenesis looking from the bottom up, then cognitive neuroscience, systems-level neurobiology, and the tools of neuroimaging represent critical tools looking from the top down. These areas of neuroscience are helping us move beyond first-approximation models of brain function in which specific brain regions were correlated with particular behavioral functions. Such narrow, almost "phrenological" views are derived from the examination of individuals with strokes, tumors, and other brain lesions; experimentally from lesions made in animals; and from early techniques of data analysis in neuroimaging that focused narrowly on regions of maximal stimulus-induced change in brain activity. The localized regions identified by these approaches likely represent critical nodes in brain circuits. We are, however, likely to obtain somewhat different, and ultimately more satisfactory information if we rephrase our experimental goals. We want to understand how mood states are represented in the brain, how genes and environmental factors during development affect the regulation of mood—and its representation in the brain. We also want to understand how salient stimuli affect mood at both brain and experimental levels in health and disease. Such inquiries require that we approach the brain as a parallel-distributed information processor rather than as a collection of specialized regions. The pathophysiologic abnormalities involved in disorders of moods may reflect subtly abnormal functioning of entire circuits as much as abnormalities within any given brain region that forms part of a circuit. Clinically we wish to be able to use neuroimaging to detect significant differences in circuit function that predict different stages of bipolar disorder, and to use imaging data as surrogate markers in clinical trials of pharmacotherapies or psychotherapy—whether for treatment or for preventive interventions.

Of course, understanding the representation and regulation of mood in the brain is very difficult. One of the great advances in behavioral neuroscience during the past decade was the initial identification of circuits involved in emotion. This was accomplished using tract tracing, physiology, lesions in animal models, and most recently, neuroimaging in humans. The best-understood circuits are, arguably, those involved in fear (Davis 1998; LeDoux 1998). The investigation of emotions such as fear is facilitated by the fact that emotion represents a rapid and transient response to environmental stimuli, and by the fact that emotions such as fear have been conserved across evolution and, thus, may be studied with some confidence in animal models. Thus, brain circuits that are involved in behavioral and physiologic responses to fearful stimuli have been identified. These "fear" circuits involve pathways from the sensory thalamus and sensory cortices, to the association cortex, from there to input and output nuclei within the amygdala, and then to effector sites in regions of the hypothalamus and periaqueductal gray matter (Fanselow and LeDoux 1999). The identification of the neural substrates of fear has made it possible to shape hypotheses concerning anxiety disorders (Coplan and Lydiard 1998). Unfortunately, the case is far different for the study of mood. Whereas emotions are transient and often stimulus bound, mood represents the long-term and predominant emotional state of an organism. Although there is no reason to doubt that animals experience changes in predominant emotional states, it is very hard to discover incisive ways of determining what they are. An important goal for the research community is to develop better empirical data, perhaps in animal models and certainly in humans, of the circuitry that regulates mood and to develop better theoretical models of mood regulation.

The relationships between emotion and mood comprise a further important but understudied area for research in bipolar disorder. Although mood is often considered a tonic affective state that is relatively unrelated to specific events, little research has explored systematically the possible influence of intense or repeated evocations of emotions in influencing mood states. Thus, problems of emotion regulation—the failure to recover a moderate affective state after a highly pleasant or unpleasant emotional experience—may represent an important aspect of mood fluctuations. Research on emotional dysregulation and its relation to mood states in health and in mood disorders is potentially highly informative.

Another potentially fruitful avenue of research that will be possible once we understand the circuitry underlying mood regulation, and have animal models, will be to study the changing expression patterns of genes and, ultimately, of proteins within those circuits as mood states change. A benefit of current genetics research will be large-scale characterization of gene transcripts expressed in the hu-

man brain and their protein products. This involves isolating a messenger RNA (mRNA) from tissue, and then reverse transcribing it into DNA, a process that produces a DNA complementary to—thus, "cDNA"—the mRNA transcript found in the tissue. The NIH is currently working to create a "gold standard" set of cDNAs that contain the entire protein sequence of thousands of mammalian genes ("full-length cDNAs"; Strausberg et al 1999). These resources will be invaluable tools for functional studies to understand how proteins function and interact in the brain to produce bipolar disorder. New genomic technologies, like DNA chips, will permit simultaneous analysis of the expression patterns of thousands of genes across multiple brain circuits and brain states (Lander 1999; Watson and Akil 1999). Salient differences in expression of particular gene products may give clues that lead to the development of novel treatment interventions.

Animal Models

Bottom-up genetic information and top-down information about behavior and neural circuits must come together if we are to develop even partial animal models of bipolar disorder. It is not likely that we can develop ideal models of bipolar disorder in animals such as rodents, which have a relatively small prefrontal cortex compared with ours and very different behavioral repertoires; however, it is distinctly possible that as we discover genes that confer risk for bipolar disorder in humans we may be in a position to create transgenic mice that express one or more human risk alleles and develop animal models that express components of the phenotype. Understanding where, when, and how these genes operate in the brain will bring together molecular-, cellular-, and systems-level neurobiology in the service of understanding pathophysiology.

Recent research with animal models has, in fact, begun to identify brain structures involved with relatively protracted affective states. For instance, the bed nucleus of the stria terminalis appears to mediate a sustained potential for heightened reactivity to sudden aversive stimuli, prompting the hypothesis that this may represent an animal model of anxiety (as opposed to more discrete fear states). Further, considerable recent research in both animal and human models has delineated the importance of such structures as the nucleus accumbens and ventral tegmental area and areas of the prefrontal cortex in maintaining positively motivated behavior for both short-term and sustained behavior (Depue and Zald 1993). Although such models are only at the beginning stages of development, they illustrate the potential for further advances in studying the neural circuitry of mood.

Pharmacologic Treatment Development

At the core of modern pharmacologic treatment development is the idea of validated drug targets. Such targets are molecules, most often proteins that are either directly involved in disease pathogenesis or form part of a pathway that strongly influences disease pathogenesis. Important drug targets from other fields of medicine are hepatic hydroxymethyl glutaryl coenzyme A (HMG CoA) reductase, the rate-limiting enzyme in cholesterol biosynthesis, and cyclo-oxygenase 2 (COX2), an enzyme induced at the site of inflammation that produces proinflammatory prostaglandins. Genes for both of these enzymes have been isolated and cloned, and expressed in systems that can be used for high throughput screens of inhibitor compounds. Inhibitors of HMG CoA reductase were discovered and gave rise to the family of "statin" drugs, which now are used widely to reduce levels of low-density lipoprotein cholesterol. Inhibitors of COX2, which are marketed for the treatment of arthritis and inflammation, have advantages over older, nonselective, nonsteroidal anti-inflammatory agents, which also inhibit COX1, found in the gastrointestinal tract, leading the older drugs to increase risk of peptic ulcers. An exciting development is the ongoing sequencing of the entire genomes of pathogens ranging from human immunodeficiency virus to mycobacteria tuberculosis. As a result of such advances, specific bacterial and viral proteins involved in pathogenesis or the growth and reproduction of micro-organisms can be targeted. With observation of mutations in proteins that correlate with resistance to antibiotic and antiviral agents, better drugs can be developed.

Drug targets in psychiatry to date have not resulted from an understanding of pathogenesis, but rather from an analysis of the mechanisms of action of pre-existing drugs. Although this approach has resulted in a very useful pharmacologic armamentarium to treat mental disorders, including bipolar disorder, it has not produced treatments that can yield cures or prevention. To move beyond drug targets derived from the action of existing treatments to targets related to pathophysiologic processes requires the tools of neuroscience and genetics.

An exciting immediate example of the utility of these disciplines in developing drug targets may lead to new treatments that would slow or halt progression of Alzheimer's disease (Haass and DeStrooper 1999; Selkoe 1999; Vassar et al 1999). To summarize this story briefly, disparate lines of research have pointed to the likelihood that a small fragment of the β-amyloid precursor protein (a specific form of the so-called Aβ fragment) is pathogenic in Alzheimer's disease. Much important biochemistry led to the identification of this fragment, but the major breakthroughs arguably came from genetics. Whereas the

common varieties of Alzheimer's disease appear to be genetically complex—that is, resulting from multiple genetic loci (including the ApoE locus) and nongenetic factors—a small percentage of familial Alzheimer's disease of early onset results from Mendelian transmission; in these cases, the dominant inheritance of a single locus is sufficient to produce illness. Genetic linkage studies in early-onset families identified multiple mutations in three different genes, the β-amyloid precursor itself and genes encoding the previously unknown proteins presenilin 1 and presenilin 2.

It appears that the β-amyloid precursor protein can be cleaved in three positions to produce different fragments. These are then released into the extracellular space where, under normal circumstances, they may be involved in cellular growth and maintenance; however, the Aβ fragment has a tendency to precipitate out and form pathogenic amyloid deposits. Each cleavage site involves a different protease—since the fragments are ultimately secreted, these protein-cleaving enzymes are referred to as the α, β, and γ secretases. If the β-amyloid precursor is cleaved by the α secretase, the resulting fragment is not pathogenic. It is the action of the β and γ secretases that together release the Aβ fragment that may lead to amyloid deposition. The little understood γ secretase recently has been thought perhaps to be presenilin 1 or else closely associated with it. The mutations that produce early-onset familial Alzheimer's disease bias these processes toward the production production of pathogenic Aβ fragments. It now appears likely that other genetic variants that have been implicated in late-onset Alzheimer's disease, such as ApoE4 and certain α_2-macroglobulin alleles may impact the metabolism of β-amyloid and its cleavage products as well. This information has led to a great race among pharmaceutical companies to produce inhibitors of the β and γ secretases.

Although this β-amyloid story is not yet proven with certainty, and there are other candidate pathways for intervention based on another aspect of Alzheimer's pathology—neurofibrillary tangles—these two secretase molecules have become important drug targets, the inhibition of which would interrupt the pathogenesis of Alzheimer's disease. Should safe and effective inhibitors be found, we would have truly incredible new weapons to alter the course of or even prevent Alzheimer's disease.

The National Institute of Mental Health has been one source of support for Alzheimer's disease genetics research, and we are proud of our contributions. We invest on a considerably larger scale in research on the genetics of bipolar disorder, and also of early-onset depression, schizophrenia, and autism. These are disorders in which, in aggregate, genes have a pronounced role in pathogenesis. If there are families in which these disorders are caused by single genes, we have yet to isolate them. More likely, the genetics of these disorders will be much more complex than those that characterize the early-onset Alzheimer families and that led to the breakthroughs outlined above. Nonetheless, by finding vulnerability genes we hope to be pointed toward actual pathogenic pathways into which we can intervene directly. Also, by determining when in brain development these genes are active, we will be better able to time our interventions.

Development of Psychosocial Interventions

While focusing on the identification of new drug targets we must not neglect the development of specific psychosocial therapies for bipolar disorder. One obvious area in which more potent psychosocial interventions are needed is the realm of treatment adherence. This is a particularly difficult problem in bipolar disorder because of the fact that during manic episodes people often feel well or even better than well and see no need to take medicine; however, many relapses relate to termination of medical treatments during periods of relative stability or early relapse. The development of psychosocial interventions that might improve adherence must involve targeting not only individuals but also families or peer groups. Several promising interventions have addressed these various groups (Miklowitz and Goldstein 1997; Simoneau et al 1999) and demonstrated efficacy in reducing symptoms, preventing relapse, and improving adherence to medications (Cochran 1984; Frank et al 1997). It is imperative to build on these leads—that is, study their generalizability and develop new treatments that will not only deal with cognitive and affective problems but also provide optimal family support and education. As with all interventions, we also need to refine our concept of desired outcomes and ensure that we can measure them appropriately.

Unfortunately, relative to other foci of treatment research for bipolar disorder within NIMH's grant portfolio, the development of psychosocial interventions has stagnated. One way of reinvigorating this important area will be to bring new information from basic behavioral science on cognition, emotion, and relationships to bear on the practical problem of psychosocial therapy development. We plan, in the coming year, to develop programs to encourage interdisciplinary interactions from basic behavioral science to public health–relevant applications, analogous to our attempts to facilitate translation from basic neuroscience to the study of disease processes and pharmacologic treatment development.

Clinical Trials

The National Institute of Mental Health has received a dearth of applications for initiation of treatment trials in

bipolar disorder. Anecdotal evidence indicates that part of this drought results from difficulties in peer review of applications related to the difficulty of achieving similar rigor in the study of clinical treatments of bipolar disorder compared with disorders such as social phobia or moderate depression. Unlike the latter disorders, individuals with bipolar disorder have an extremely unstable baseline of symptoms and functioning. Thus, for example, in a trial of antimanic therapy an individual might develop a severe depression, necessitating the use of antidepressant treatments. This frequent occurrence is clearly confounding with respect to the initial goals of the trial, but we cannot have standards of review that exclude research on disease entities that fall outside the bounds of certain "better behaved" illnesses. At the suggestion of members of our National Advisory Mental Health Council we will form a small working group to address peer review issues with respect to clinical trials and bipolar disorder. The dearth of trials, however, has left us far from where we could be at this moment in history.

The problem is well illustrated with a history of use of the anticonvulsant carbamazepine in treating manic–depressive illness. This drug came into use in manic–depressive illness following an early report of Japanese investigators (Okuma et al 1973) and the amplification of their findings in the United States. Whereas, in aggregate, there were convincing data that carbamazepine was effective as a short-term antimanic agent, there remain no adequately designed trials of carbamazepine in long-term mood stabilization and prophylaxis. Absent clear data, this drug has slowly faded from favor, especially given the fact that valproic acid has emerged as a more tolerable and apparently more efficacious alternative for long-term prophylaxis. There are now several promising new anticonvulsants, including lamotrigine and gabapentin. In the belief that we cannot permit time to pass before mounting adequate trials and cannot rely on the kinds of small, often poorly designed trials that too frequently characterize this field, NIMH has initiated the NIMH Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD) trial (Epidemiology Data Center 2000). One of the largest clinical trials ever undertaken for this disorder, STEP-BD involves 20 sites around the country where some 5000 patients with bipolar disorder will be observed for up to 5 years. The most effective medication and psychosocial interventions for the prevention and treatment of depression, mania, and mood cycling will be evaluated under real-world conditions, including targeted randomized treatment choices for some 1500 patients. This trial will help assure that we have the knowledge to offer optimal treatment options in diverse real-world treatment settings to the wide range of individuals suffering from bipolar disorder.

In addition to testing new therapies in adequate numbers of individuals, the STEP-BD trial is one of a new generation of clinical trials introduced into the NIMH clinical program during the last 2 years that is noteworthy on several counts. Prior clinical trials supported by NIMH tended to be extremely well-designed, placebo-controlled randomized clinical trials. Although we expect to continue supporting such tests of treatment efficacy, these trials have certain shortcomings, particularly given that they traditionally have been the last step in the study of treatment intervention. Rigorously controlled efficacy trials tend to be short term; to enroll highly selected populations based on age restrictions and lack of comorbid mental or physical disorders or substance use disorders; and to be conducted within a narrow range of settings—generally academic health centers and their related clinics. Although such trials are an essential step in demonstrating the intrinsic efficacy of the treatment, they are not readily generalizable to broader populations and settings, and therefore do not always convince insurers or employers. Just as importantly, efficacy studies are unlikely to provide the full range of information needed by practitioners or consumers. Most people with bipolar disorder find their circumstances dissimilar to those of patients enrolled in traditional efficacy trials. For this reason, the STEP-BD contract has few exclusion criteria and longer term treatment and follow-up periods, assesses functional outcomes as well as symptom reduction, and will be conducted at diverse sites, which should allow generalizability to much of the American health care system. While this is an important first commitment, this emphatically will not be the only NIMH investment in bipolar disorder treatment trials. We strongly welcome treatment applications addressing many issues that will not be settled by this trial.

Among the more significant gaps in treatment knowledge that must be filled involves information on children and adolescents with bipolar disorder. Because differences in development stage clearly have implications for treatment efficacy and safety, data from adults do not necessarily apply to younger patients. Ongoing multisite studies funded by NIMH are investigating the value of long-term treatment with lithium and other mood stabilizers in preventing recurrence of bipolar disorder in adolescents. Beyond the urgently needed information they will provide about basic safety and efficacy, studies of bipolar illnesses in children and adolescents have examination of factors that predict outcomes and adherence to treatment among their priorities.

A final issue, and one that brings us full circle to basic science, is the lack of good biomarkers or surrogates for changes in pathophysiology that would provide measurable objective variables for clinical trials. This leads back to the area of neuroimaging discussed above and the requirement that we begin to understand the circuits underlying mood regulation in the brain and what goes

wrong in the different stages of bipolar disorder. Ultimately, it is to be hoped that imaging will provide robust surrogate markers reflecting the abnormal physiology produced by mania, depression, and other symptoms of bipolar disorder. Specific and informative biomarkers can complement subjective rating scales in the evaluation of treatments and will make our clinical trials far more efficient as well as more convincing to individuals involved in setting health care policy.

Summary

We have much yet to accomplish in research on bipolar disorder. We must find vulnerability genes. We must identify the circuits that regulate mood, emotion, energy, and other relevant functions that are affected in bipolar disorder, and we must determine what goes wrong in those circuits during mania, depression, and other aspects of this illness. We will need to translate findings in basic neuroscience, genetics, and basic behavioral science into diverse clinical applications: novel treatments, diagnostic tools, epidemiologic approaches that could lead to preventive interventions, and surrogate markers for clinical trials. We must develop improved psychosocial interventions and test both pharmacologic and psychosocial treatments in trials that, simultaneously, improve the quality of care available and convince insurers and employers that these treatments are of substantial benefit and cost effective. The agenda is ambitious, but entirely feasible, given the scientific tools and technologies that are currently available or on the horizon. The National Institute of Mental Health is newly recommitted to harnessing these tools and technologies for the benefit of people with bipolar disorder.

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